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LANDO & ANASTASI, LLP
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@LALaw.com
gengelson@LALaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/749,962	GOVARDHAN ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,7-10,17-22 and 60-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,7-10,17-22 and 60-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/12/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/12/2010 has been entered.

Applicants' amendment canceling claims 1-3, 5-6, 11-16, 23-59; amending claims 4, 7, 8, 9; and adding new claims 81-84 in the paper of 05/12/2010 is acknowledged.

Claims 4, 7-10, 17-22 and 60-84 are pending in the instant office action and will be examined herein.

Information Disclosure Statement

2. The information disclosure statement (IDS) filed on 05/12/2010 has been reviewed, and its references have been considered except for those which have been lined through. A copy of Form PTO/SB/08 is attached to the instant Office action.

Claim Objections

3. Claims 4, 7-10, 17-22 and 60-84 are objected to because of the following informalities:

(a) Claims 4, 7, 8 and 9 (Claims 10, 17-22 and 60-84 dependent therefrom) recites "A polyarginine containing crystal of human growth hormone (hGH)...". Since the instant invention is directed to a hGH protein in crystalline form; and "A polyarginine containing crystal of human growth hormone (hGH) comprising hGH" is redundant with the recitation of "comprising polyarginine and hGH" in terms of contents of claimed crystal, the Examiner suggest amending claims to recite ---A crystal of human growth hormone (hGH) comprising hGH and an excipient of polyarginine (or polyarginine polymer), wherein....----; and change its dependent claims accordingly, to improve the format of claims.

(b) Claim 7 (Claims 10, 17-19, 22 and 60-63, 68-72, 76-80, 84 dependent therefrom) recites "$T^{90\%}$"; whereas, the instant specification recites "$T_{90\%}$" which indicates how long the drug remains in the serum for longer (see top of page 55). The use of term "$T^{90\%}$" should be consistent through out the application including claims.

(c) Claim 17 (Claims 18-22 dependent therefrom) 22 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim; for reciting "and an excipient". Since polyarginine in claims 4, 7, 9 or 9 is a species from a genus of excipient, claims 17-20 and 22 are not further limiting from claims 4, 7, 9 or 9.

(d) Claims 17-22 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, the polyarginine is a species of excipient in claims 17-22 which requires to at a molar ratio of hGH:excipient of 1:10 to 1:0.125. The molecular weight of hGH with N-terminal Met is 22 kDa (see attachment of Compute pI/Mw). The molecular weight of polyarginine ranges from 15,000 kDa to 60,000 kDa (see instant specification page 19, paragraph 0066). Thus, said molar ratio of 1:10 to 1:0.125 translates into the range of 22:150,000 kDa to 22:1875 kDa (i.e., 1:68 to 1:85 by weight/weight). The range of 1:68 to 1:85 is outside the range of polyarginine ratio of "12:1 to 3:1 (w/w)" recited in their independent claims 4, 7, 8 and 9; thus, claims 17-22 do not further limit claims 4, 7, 8 and/or 9. In the interest of advancing prosecution, Claims 3-5 have been interpreted as being dependent from Claim 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 9, 17-22, 60-63, 66, 69-72, 74, 77-80 and 82 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 (Claims 17-22, 60-63, 66, 69-72, 74, 77-80 and 82 dependent therefrom) recites "wherein said bioavailability is measured by area under curve (AUC) of total *in vivo* hGH serum concentration for said soluble hGH and said hGH crystal". It is wholly unclear how a bioavailability *in vivo* hGH in serum would be measured by AUC when AUC is measured by UV-VIS spectrophotometer at certain wave length *in vitro*. Because a serum contains many proteins and molecules that give signal at UV range, for example, it would not correctly reflect the concentration of hGH *in vivo*. It appears that AUC by UV-Vis spectrophotometer is used to calculate solubility of hGH crystal in vitro using only a soluble hGH as shown in Example 5. However, the term "bioavailability" applies to both soluble and crystal form of hGH, once it is introduced to a patient, since a crystalline form of hGH would to be solublized inside the patient. Thus, if the identical dose is used, the amount of bioavailability is same and can't be at least 50% or more.

Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim(s) 4, 7-10, 17-22 and 60-84 are rejected under 35 U.S.C. 112, first paragraph, **written description**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both Lily and Enzo Biochemical to methods of using products, wherein said products lack adequate written description. While in

University of Rochester v. G.D. Searle & Co. the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from Enzo Biochemical (see above).

MPEP 2163.II.A.2.(a).i) states, "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention".

In this case, the specification discloses the following representative species of crystalline human growth hormone (hGH; even if, it is assumed that the amino acid sequence of hGH consist of 191 native hGH or with additional Met at the N-terminal residue) prepared according to instant Examples 1-4, 6-8 and 10-14 (specification pages 40-51) and soaking in a polyarginine, thereby forming a hGH:polyarginine crystal complex. The breadth of claims encompasses a genus of hGH co-crystal comprising hGH, polyarginine polymer and any other additives (in view of comprising); wherein said hGH is the 191 amino acid sequence of native hGH or with additional Met at the N-terminal residue. However, the instant specification do not describe adequately claimed

genus of co-crystallization of hGH:polyarginine resulting a hGH:polyarginine co-crystal with optionally having any other additives for a function of forming claimed genus crystalline form of hGH. Furthermore, the instant specification disclose that hGH was purchased from "BresaGen Ltd." (see page 40, middle), wherein there are many known hGHs such as polypeptide with "isoforms with molecular masses of 5, 17, 20, 22, 24, 36 and 45 kDa" according to instant specification page 11, middle; thus, failed to describe which hGH is used in the instant examples; in turn failed to describe a single example sufficiently. Even if, said hGH is limited to well known native hGH (which consist of 191 native hGH or with additional Met at the N-terminal residue), these disclosed species fail to reflect the variation among the claimed members of the genus, wherein the variation in added agents presented in claimed hGH co-crystallized with polyarginine and optionally with any other agents. Sorensen et al. (1998, US Patent 5,849,700 - cited previously) disclose one example of native hGH (with 191 amino acid sequence) crystal which can be soaked or mixed with polyarginine. According to MPEP 2163.II.A.2.(a).ii), “For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus”. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Because the art of protein crystallization is highly unpredictable (see below discussion regarding the state of the art of protein crystallization), the specification’s disclosed representative species fail to describe all complexes, compositions, and methods as encompassed by the claimed genus. The instant specification and prior art failed to disclose adequate correlation between structure (crystal comprising hGH:polyarginine with any other

agent(s) (and do not disclose single example of co-crystal of hGH in the presence of polyarginine) and the function of forming a claimed hGH crystal as described above. The claimed genus of crystal or co-crystal comprising hGH:polyarginine encompass widely variant species and given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

6. Claims 4, 7-10, 17-22 and 60-84 are rejected under 35 U.S.C. 112, first paragraph, **scope of enablement**, because the specification, while being enabling for a crystalline human growth hormone (hGH; even if, it is assumed that the amino acid sequence of hGH consist of 191 native hGH or with additional Met at the N-terminal residue) prepared according to instant Examples 1-4, 6-8 and 10-14 (specification pages 40-51) and soaking or adding with a polyarginine solution (emphasis added), thereby forming a hGH crystal composition comprising hGH:polyarginine; **does not** reasonably enable genus of claimed crystal of hGH:polyarginine with any other agent; or the co-crystallized hGH polypeptide of instant claims in the presence of polyamine; wherein said hGH is the 191 amino acid sequence of native hGH or with additional Met at the N-terminal residue.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims…and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims…claims are to be given their broadest reasonable interpretation that is consistent with the specification."

The breadth of claims encompasses a genus crystallized hGH:polyarginine polymer with any other agents (protamine, or HEPES for example) or co-crystallized hGH in the presence of polyarginine polymer and any other additives (in view of

comprising); wherein said hGH is the 191 amino acid sequence of native hGH or with additional Met at the N-terminal residue.

The broad scope of claimed crystals is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to being enabling for a complex of crystalline or co-crystallized human growth hormone (hGH):polyarginine and optional agent(s) according to instant specification and prior art.

The nature of the invention: The invention is drawn to a hGH crystal soaked in or mixed with polyarginine polymer to form complex after hGH has been crystallized according to the instant Examples 1-4, 6-8 and 10-14 (specification pages 40-51); assuming that the amino acid sequence of hGH consist of either 191 amino acid long native hGH or with additional Met at the N-terminal residue

As noted in the specification, the invention involves protein crystals. At the time of the invention, methods of protein crystallization were well-known in the art. However, the ability to crystallize a given protein was, at the very least, challenging and unpredictable to a skilled artisan as even minor alterations in the amino acid sequence of the polypeptide, ligand, and/or conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: According to MPEP 2164.03, "what is known in the art provides evidence as to the question of predictability…in applications directed to inventions in

arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims".

At the time of the invention, the state of the art regarding protein crystallization to achieve isomorphous protein crystals was difficult and highly unpredictable. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1999; cited in the 6/27/08 IDS) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20, 2001), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Also, Wiencek (*Ann Rev Biomed Eng* 1:505-534, 1999) teaches that "[p]rotein solubility will change

dramatically as pH is altered by ~ 0.5 pH units…some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom).

Additionally, Buts et al. (*Acta Cryst* D61:1149-1159, 2005) teaches that "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization." "Five naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution." Specifically, the reference of Buts *et* al. teaches that the F17e-G and F17f-G adhesins differ in only one amino acid from the F17c-G adhesin, Arg21Ser and His36Tyr, respectively, and yet these proteins that are 99% identical in sequence resulted in different crystal forms with distinct diffraction properties (see Tables 1-3).

Skarzynski et al. (Acta Cryst D62:102-107, 2006) teaches "crystals of complexes obtained by compound soaking may become damaged, change their diffraction properties or even change the space group during the soaking experiment!" (p. 103, right column, middle). Skarzynski et al. further teaches that binding of potent compounds during soaking often causes complete or partial disruption of the crystal lattice, poorly soluble compounds may interfere with the diffraction pattern of the protein crystal sample, and very often no binding is observed for active compounds, despite their potency under biochemical or biological assay conditions" (p. 104, left column, middle). The teachings of Skarzynski et al. are supported by applicant's specification,

which teaches "Attempts to soak the GDP-4-keto, 6-deoxy mannose substrate or GDP into the crystals failed" (p. 15, top).

Even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot, *Cell. Mol. Life Sci*. 2004, 61: 525-536) and currently there are no directed methods which makes this process any easier or more predictable. Thus, each protein that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see also Weber, *Methods in Enzymology*, 1997, Vol. 276, pp. 13-22; cited in the 6/27/08 IDS). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a role in obtaining crystallization

conditions despite the extremely high skill level of those in the art (see Drenth, *supra,* Cudney, *Rigaku Journal*, 1999, Vol. 16, No. 1, pp. 1-7).

McPherson (*Eur. J. Biochem.* 189:1-23, 1990) teaches (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual."

Thus, in view of these teachings, a skilled artisan would recognize there is a high level of unpredictability in making a diffraction-quality protein crystal.

The amount of direction provided by the inventor; The existence of working examples: According to MPEP 2164.03, "if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling".

The specification discloses methods for preparing a complex of crystalline human growth hormone (hGH), although it does not disclose which hGH polypeptide is used in said crystallization method, and soaking or mixing with polyarginine polymer. Sorensen et al. (1998, US Patent 5,849,700 - cited previously) disclose one example of native hGH (with 191 amino acid sequence) crystal which can be soaked or mixed with polyarginine.

However, these working examples fail to provide the necessary guidance for making the entire scope of complexes, compositions and methods as broadly encompassed by the claims. For example, the specification fails to provide guidance regarding alterations in, *e.g.,* the amino acid sequence, ligand, any agent(s) and crystallization conditions, *e.g.*, protein concentration, buffer (components, concentrations, and pH), and temperature, with an expectation of obtaining a hGH crystal or co-crystal of hGH:polyarginine polymer; optionally with other polymers, for example.

While it is acknowledged that the specification discloses crystallization of a certain hGH purchased from BresaGen Ltd, the specification fails to disclose which hGH

polypeptide was obtained or prepared such that a skilled artisan could replicate this process forming a claimed genus crystal comprising hGH:polyarginine or co-crystal thereof.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallography were known at the time of the invention, it was not routine in the art to make all hGH:polyarginine crystals as encompassed by the claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance and direction, the determination of crystallization condition to form claimed genus hGH crystal is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 4, 7-10, 17-22 and 60-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorensen et al. (1998, US Patent 5,849,700 - cited previously) in view of Singh (US Patent 5,788,959, Aug. 4, 1998) and DeFelippis et al. (1998, J. Pharm. Sci., vol. 87, pages 170-176, as cited previously).

The rejection was stated in the previous office action as it applied to previous Claims 4, 7-10, 17-22 and 60-80. In response to this rejection, applicants have amended claims 4, 7, 8, 9; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that Sorensen et al. in view of Singh and DeFelippis et al. do not teach newly added limitation of "the hGH:polyarginine ratio is 12:1 to 3:1 (w/w)"; see top of page 9, Remarks filed on 5/12/2010. Applicants also argue DeFelippis does not remedy these defects and teach use of protamine with insulin which is unrelated to hGH; and argue DeFillipis only disclose molar ratio for insulin:protamine of 8:1; thus, in combination of Sorensen et al. in view of DeFelippis et al. do not teach or suggest hGH with polyarginine having said ratio above.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Contrary to applicants' argument, the addition of polyarginine polymer or protamine as a stabilizer to a protein therapeutic agent is well known at the time of instant invention in view of teachings of Singh and DeFelippis et al. as noted previously (and below); thus, the use of polyarginine and/or protamine is not limited to only insulin in view of Singh and DeFelippis et al. As noted previously (see bottom of page 4 in final office action mailed on 4/13/2009), Sorensen et al. disclose that "animal growth hormone may be stabilized with various stabilizers to give decreased formation of insolubles and preservation of the soluble activity in aqueous environments" (see bottom of §2); wherein the stabilizer includes "polyarginine" (see §3, line 11). Thus, one skilled in the art would be motivated to add polyarginine and/or protamine into a hGH protein regardless of its form when hGH is to be used as therapeutic agent with a reasonable expectation of success. Also, Singh teach that "preferably about 0.1" and "about 0.5" of polymers weight ratio compared to the therapeutic protein (i.e., 1: 0.1 of protein:polymers, that is equivalent to 10: 1 (or 5:1 using the ratio of said "0.5")); meeting the newly added limitation in claims 4, 7-9 and 81-84. The motivation to do so is that "If the concentration of the two polymers are too high, they may not be injectable", wherein injection is more convenient to utilize (see column 5, lines 10-15).

As similarly noted in previous office action, Sorensen et al. teach a pharmaceutical formulation comprising a crystal of human growth hormone (hGH, 1.13

mg/ml in §10, line 23) (see Abstract and Example 4 in §13); wherein the “Human growth hormone consists of 191 amino acids" (see column 1, lines 20-21).

Sorensen et al. do not teach a composition having a polyarginine as part of the hGH crystal.

Singh teach a drug delivery device comprising "solution of a negatively-charged water-soluble polymer solution and a positively-charged water-soluble polymer" (i.e., a molecule encompassed by the instant recitation of "a cation"; such as polyarginine which has + charge(s) in normal physiological pH) in the presence of a pharmaceutically active ingredient (see Claim 1); wherein the positively-charged water-soluble polymer is polyarginine (see Claim 6) and the pharmaceutically active ingredient is human growth hormone (see Claim 11) which is used for the sustained release of a pharmaceutically active ingredient (see §1, lines 5-6). Singh teach the preferable ratio, by weight, of polymer to pharmaceutically active hGH, for example, "preferably about 0.1" and "about 0.5" of polymer weight ratio compared to the therapeutic protein (i.e., 1: 0.1 of protein:polymers, that is equivalent to 10: 1 (or 5:1 using the ratio of said "0.5")) because if the concentration of the two polymers are too high, they may not be injectable, wherein injection is more convenient to utilize (see column 5, lines 10-15).

Also, Sorensen et al. disclose that "animal growth hormone may be stabilized with various stabilizers to give decreased formation of insolubles and preservation of the soluble activity in aqueous environments" (see bottom of §2); wherein the stabilizer includes "polyarginine" (see §3, line 11).

Sorensen et al. and Singh do not teach the limitation of an excipient, e.g., protamine, (Claims 20-21) and/or said excipient having a molar ratio of hGH: excipient of 1:10 to 1:0.125 (Claim 18).

DeFelippis et al. disclose the protamine suspension of LysPro (a human insulin analogue) having an “8:1 molar ratio” (equivalent to 1:0.125) of LysPro to protamine (see bottom of left column, page 173 for pharmaceutical preparations of insulin).

Therefore, It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a pharmaceutical composition comprising the hGH crystal of Sorensen et al. by adding polyarginine as a stabilizer with a reasonable expectation of success that the formulation would co-crystallize or said crystal could be soaked with the polyarginine or protamine with ratio of 10:1 or 5:1 by w/w as suggested by Singh. One would have been motivated to add a polyamine to the human growth hormone crystal of Sorensen et al. as taught by Singh who teach the polyarginine allows sustained release of a pharmaceutically active ingredient "over a prolonged period of time" (see §2, line 34). The recited crystal characterization of a release profile in Claims 7-9 are inherent characteristics of the pharmaceutical composition comprising the polyamine and the human growth hormone crystal of Sorensen et al. Also, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include hGH of Sorensen et al. to a protamine suspension (e.g. 1:0.125 ratio as taught by DeFelippis et al) with reasonable expectation of success because the protamine is the most commonly used intermediate-acting suspension according to DeFelippis et al. (see bottom of left column, page 170). One would have been

motivated to include protamine into said hGH crystalline suspension since the protamine excipient prolong a pharmaceutical composition in patients and increase the duration of its action (see top of right column, page 170 of DeFelippis et al.) Thus, the invention taken as a whole is *prima facie* obvious.

It is noted that Claims 60, 61 and 63 (Claims 69, 70, 72, 77, 78, 80 dependent therefrom) are product by process claims. The factors to be considered for a product-by-process are summarized in MPEP 2113. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983) and Ex parte Gray, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989). It is also noted the characterization(s) recited in instant claims 7-9 does not contribute a structural limitation of claimed hGH crystal but they are inherent features of hGH when it is in crystalline form as evidenced by the instant specification. Furthermore, according to MPEP 2144.05 [R-5] II, A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456,

105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Maintained-Double Patenting

8. The previous provisional rejection of Claim 4 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 7, 9 and 10 of copending Application No. 11/169,956 (US 2006/0008532) is maintained.

Applicants defer addressing this rejection because neither application has issued as a patent and no conflicting claims have been patented (see

Applicants' arguments have been fully considered but are not deemed persuasive to withdraw instant rejection for the following reasons. Because neither application have been patented and both are still pending, the instant rejection is provisional and will be held in abeyance until such time as a full non-provisional decision can be rendered.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 10AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656